Scientists identify gene target to boost effectiveness of cancer immunotherapy

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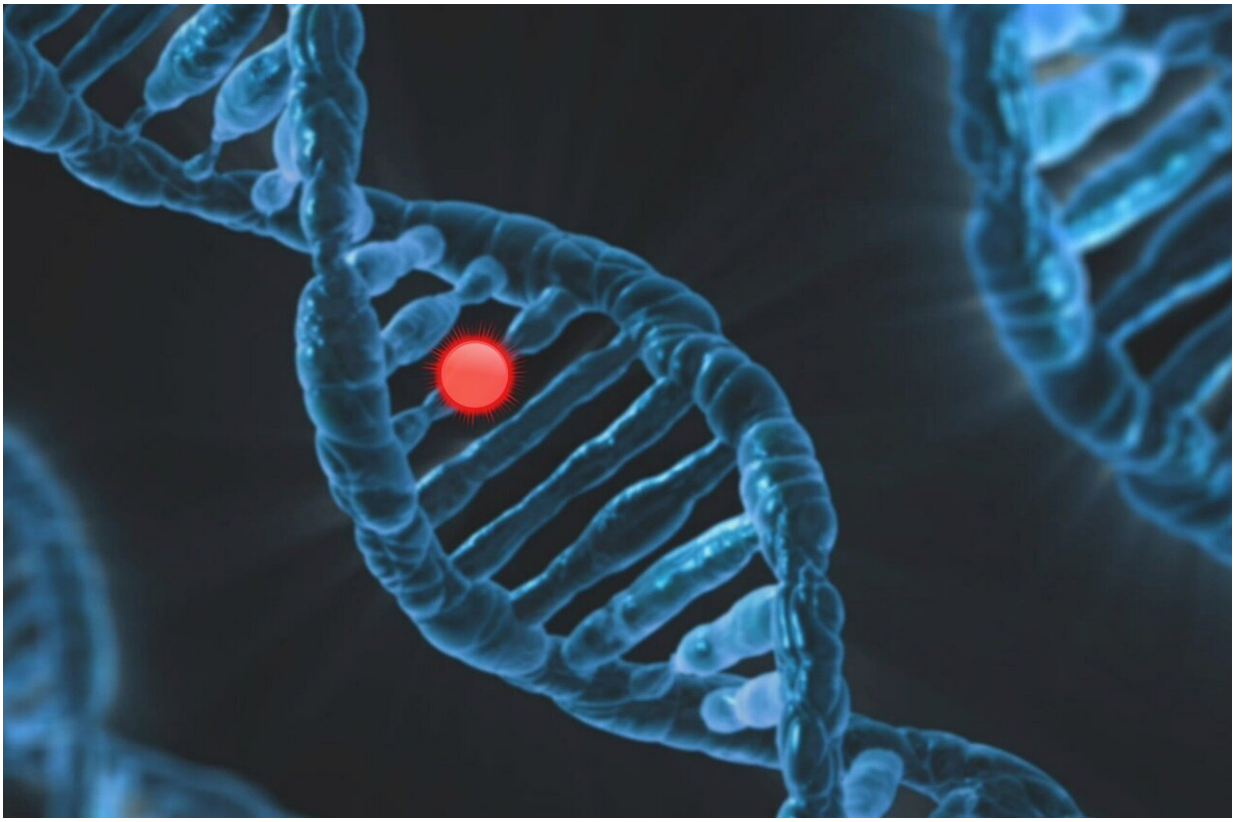

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Immune checkpoint inhibitors are important medications that boost the immune system's response against various cancers, but some patients' cancer cells are unaffected by the drugs or develop resistance during

treatment.

Researchers led by a team at Massachusetts General Hospital (MGH), a founding member of Mass General Brigham, and the Broad Institute of MIT and Harvard recently identified an immune evasion gene that is turned on in some of these cells, and they found that silencing the gene enhanced the cells' susceptibility to immunotherapy.

The gene codes for a protein called TANK-binding kinase 1 (TBK1), a multi-functional enzyme with an established role in coordinating innate immune responses to viruses and other invading pathogens.

In a study published in *Nature* led by senior authors Russell W. Jenkins, MD, Ph.D., an investigator in the Center for Cancer Research at MGH and an Assistant Professor of Medicine at Harvard Medical School, and Associate Member of the Broad Institute, and Robert T. Manguso, Ph.D., also an investigator in the Center for Cancer Research at MGH, Assistant Professor of Medicine at Harvard Medical School, and Associate Member of the Broad Institute, found that deleting the TBK1 gene sensitizes tumors to immune attack.

Also, in mouse models of cancer, treatment with a pharmacologic inhibitor that blocks the activity of the TBK1 protein overcame tumors' resistance to immunotherapy, without causing weight loss or other signs of systemic toxicity. This strategy also worked in novel patient-based tumor models, including what are called patient-derived organotypic tumor spheroids, or PDOTS, which are "living biopsies" that contain a patient's own cancer cells and immune cells.

Mechanistically, the team found that blocking TBK1 augments the response to immunotherapy by sensitizing tumor cells to the effects of immune molecules including tumor necrosis factor and interferon.

"It's counterintuitive that TBK1 loss would enhance immunotherapy, because this protein is generally thought to promote inflammation. Turning it off should make a tumor less sensitive to treatment, not more" says Manguso, who also co-leads the Tumor Immunotherapy Discovery Engine project at Broad. "However, we found that turning off TBK1 reprograms tumor cells' response to immune signals called cytokines, causing them to die. This latter effect turns out to be critical in this context."

"Our results demonstrate that targeting TBK1 is a novel and effective strategy to overcome resistance to cancer immunotherapy," says Jenkins. "Our work also provides a framework to evaluate other potential immune evasion targets across multiple model systems using a combination of genetic and pharmacologic tools."

More information: Sun, Y. et al, Targeting TBK1 to overcome resistance to cancer immunotherapy, *Nature* (2023). DOI: 10.1038/s41586-019-0000-0.
www.nature.com/articles/s41586-023-05704-6

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